IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: BENNEKER et al.

Title: ***4-PHENYLPIPERIDINE COMPOUNDS***

Appl. No.: 09/200,743

Filing Date: 11/30/1998

Examiner: Celia C. Chang

Art Unit: 1625

Confirmation Number: 9739

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Jose Sintas, hereby declare and state as follows:

1. I am currently employed by Noven Pharmaceuticals, Inc., which is a corporate entity related to Noven Therapeutics, Inc., the assignee of the captioned application ("the U.S. application"). I have completed a Postdoctoral Fellowship in Organic Chemistry, and have earned a Ph.D. in Organic Chemistry and a Masters in Radiochemistry. My position at Noven is Principal Scientist and my responsibilities include method development, structure elucidation of unknown degradants, etc. I have hands-on experience with FT-IR spectroscopy. A copy of my *curriculum vitae* is attached as Appendix A.

2. I have read the U.S. application and allowed claim 31. I have also read opinion 2005 UKHL 59 of the UK House of Lords of Appeal ("the UK opinion"). The UK opinion concerns the unpatentability of a Smithkline Beecham UK patent in view of a Synthon patent application that is related to this U.S. application.

3. The UK opinion characterizes in general terms the activities of two chemists who sought to make crystals of paroxetine mesylate ("PM") according to the procedure described in the Synthon application. *See, e.g.*, page 6, ¶15. The UK opinion states that crystals of PM eventually produced by the chemists did not "have the IR spectrum predicted by Synthon in Table 1," but "instead had the spectrum described in the [Smithkline Beecham patent]." *See, e.g.*, page 6, ¶15. The UK opinion states further that the "IR spectrum in Table 1 of [Synthon's] application was the result of a mistaken reading in their own laboratory." *See, e.g.*, page 7, ¶16.

4. I understand that the UK opinion may raise questions surrounding the IR data recited in allowed claim 31 of the U.S. application. However, the following demonstrates that the recited IR data correctly characterize crystals of paroxetine mesylate.

5. Crystalline PM is an active pharmaceutical ingredient ("API") that is produced for Noven by several different manufacturers. The IR spectra of crystalline PM obtained from different API manufacturers are identical, and they correspond to the IR peaks disclosed and claimed in the U.S. application.

6. The full IR spectrum of a sample lot of crystalline PM that was obtained from API manufacturer #1 located in Germany is set forth in Appendix B. The spectrum includes the IR data in graphic fashion, and also superimposes a list of peaks that were obtained by a computer-assisted peak-picking function, as is customary in obtaining IR data.

7. The full IR spectrum of crystalline PM that was produced by API manufacturer #2 located in Argentina is set forth in Appendix C, atop an IR spectrum of a standard sample of crystalline PM. As with the IR spectrum in Appendix B, certain peaks are identified numerically, as shown by the numbers superimposed on the spectra.

8. The IR spectra in Appendices B and C contain bands that are characteristic of certain structural features in PM. For instance, the absorption bands at about 1191 cm^{-1} (symmetric stretch) and 1162 cm^{-1} (asymmetric stretch) are fingerprints for the sulfonates (mesylate). A fingerprint absorption band for secondary amine salts is also observed as a broad peak in the region of 3100-2700 cm^{-1}. Notice that there are several reported peaks in this region (2849

and 3006 cm^{-1}); however it is actually a broad band. An aryl ether fingerprint band is observed at about 1031 cm^{-1} (symmetric stretch). These data confirm that the IR spectra are consistent with what someone skilled in the art would expect for PM.

9. Superimposing the spectra of Appendices B and C reveals that the full IR spectra are essentially identical. That is to say, peak positions, shapes, and intensities from each spectrum are the same.

10. Based upon my experience in IR spectroscopy, I understand that peak-picking algorithms, if they are used at all, may identify a peak in one spectrum but not the other, or attribute slightly different absorption bands to the same peak appearing in each spectrum. Such artifacts are normal, and they do not undermine a conclusion that two given IR spectra concern the same substance based upon graphical identity of the full IR spectra.

11. I therefore conclude that the IR spectra in Appendices B and C are identical and characterize the chemical structure of crystalline PM.

12. I also have considered whether the IR spectra in Appendices B and C correspond to the IR data disclosed and claimed in the U.S. application, that is, the IR peaks listed in Table 1 and recited in claim 31 of the U.S. application. These peaks are:

531, 546, 777, 838, 931, 962, 1038, 1100, 1169, 1208, 1469,
1500, 1515, 1615, 2577, 2869, 2900, and 3023 cm^{-1}.

Based upon my comparison of the disclosed/claimed IR peaks to the full IR spectra in Appendices B and C, I conclude that the claimed IR peaks characterize the same crystalline form of crystalline PM that gave rise to the appended IR spectra. For instance, for the mesylate fingerprint absorption bands at about 1191 cm^{-1} and 1162 cm^{-1}, the reported values in Table 1 are 1208 cm^{-1} and 1169 cm^{-1}. For the secondary amine salt fingerprint absorption band at about 3100-2700 cm^{-1}, the reported values in Table 1 are 2869, 2900 and 3023 cm^{-1}. For the aryl ether fingerprint band at about 1031 cm^{-1} (symmetric stretch), the reported value in Table 1 is 1038 cm^{-1}.

13. I also have examined a copy of an IR spectrum of crystalline PM that Smithkline Beecham submitted during prosecution of the European patent (EP 0970955) related to the UK patent at issue in the UK opinion referenced above. The IR spectrum ("the SKB spectrum") was submitted to the European Patent Office ("EPO") as part of an affidavit by Mr. Ian Robert Lynch, and is available from the EPO website. A copy of the SKB spectrum is set forth in Appendix D.

14. Superimposing the SKB spectrum in Appendix D with those of Appendices B and C reveals that the full IR spectra are essentially identical. That is to say, peak positions, shapes, and intensities from each spectrum are the same. I therefore conclude that the SKB spectrum in Appendix D characterizes the same crystalline form of crystalline PM as the IR spectra in Appendices B and C.

15. Comparing the disclosed/claimed IR peaks of the U.S. application to the full SKB spectrum in Appendix D, I conclude that the claimed IR peaks characterize the same crystalline form of crystalline PM as the SKB spectrum in Appendix D. For instance, for the mesylate fingerprint absorption bands at about 1192 cm^{-1} and 1163 cm^{-1}, the reported values in Table 1 are 1208 cm^{-1} and 1169 cm^{-1}. For the secondary amine salt fingerprint absorption band at about 3100-2700 cm^{-1}, the reported values in Table 1 are 2869, 2900 and 3023 cm^{-1}. For the aryl ether fingerprint band at about 1032 cm^{-1} (symmetric stretch), the reported value in Table 1 is 1038 cm^{-1}. The rest of the significant absorption bands observed in the IR spectrum in Appendix D are presented below, in comparison with those reported in Table 1:

Table 1	777	838	1038	1169	1208	2869-3023 (broad)
Appendix D	775	829	1032	1163	1192	2846-3007 (broad)

The same set of fingerprint absorption bands are present in both IR spectra.

16. My analysis here, and a review of the appended IR data, shows that the U.S. application discloses and claims IR peaks that characterize the same crystalline form of crystalline PM as is used in Noven's commercial crystalline PM products and that was the basis of Smithkline Beecham's IR spectrum.

17. I further declare that all statements made in this declaration of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of legal decisions of any nature based on them.

Date 03/06/2009 By _____

Jose Sintas, Ph.D.

APPENDIX A

JOSE A. SINTAS

SUMMARY OF QUALIFICATIONS:

- Ten years of laboratory work with extensive experience in Analytical and Synthetic Organic Chemistry.
- Working experience with Millenium, Turbochrom, ChemStation, Xcalibur, WinNMR, Masslinx; HPLC, LC/MS/PDA, GC, GC/MS.
- Experience in HPLC, GC, LC/MS Method Development and Method Validation, review and writing of Validation Protocols and Reports.
- Experience in structure elucidation of unknown Impurities using NMR, GC/MS, LC/MS etc..
- Experience setting-up, calibrating, troubleshooting and operating automated lab instrumentation that includes NMR, HPLC, GC, FT-IR, GC/MS, LC/MS and UV. Extensive knowledge of Chromatographic Separation Theory.

WORK HISTORY:

January 2006- Present **Noven Pharmaceuticals.** AR. Miami, Florida.
Principal Scientist

February 2004- January 2006 **Noven Pharmaceuticals.** AR. Miami, Florida.
Senior Scientist

Development of HPLC test methods for finished product impurity testing. Writing and performing of Validation/Transfer Protocols and Reports. Development of LC/MS and GC/MS methods for assay and use of LC/MS and NMR for structure elucidation of unknown impurities/degradants. Synthesis of impurity standards and derivatization of commercially available API for R&D use.

August 2003- February 2004 **Watson Laboratories.** R & D. Corona California.
Senior Scientist

Development of HPLC test methods for finished product impurity testing. Writing and performing of Validation Protocols and Reports. Analytical R & D project management of a NDA.

February 2002- July 2003 **Guidelines Integrated Services.** R & D. Miramar, Florida.
Senior Chemist.

Development of several HPLC and LC/MS Methods for Stability Indicating Assay, Dissolution and Chromatographic Purity of Raw material and Drug Products. Review and writing of Validation Protocols and Reports.

January 2000- **Florida International University.** Miami, Florida.

March 2002 Adjunct Faculty, Chemistry Department.

Developed methods for synthesis, chromatographic purification and spectroscopic analysis of new azulene antioxidants.
Extensive use of spectroscopic (NMR, UV, FT-IR, MS) and chromatographic (HPLC, GC) methods of analysis and structure determination, including, setting-up, calibration, validation, troubleshooting and data interpretation.
Assistant Professor in Forensic Chemistry. GC and HPLC Analysis of drugs of abuse.

ACCOMPLISHMENTS:
Developed new synthetic strategy for the preparation of novel azulene antioxidants. (See publications).
Developed methods for HPLC, LC/MS, GC/MS, UV-VIS and fluorescence analysis of a family of azulene compounds.

December 1995- December 2000 **UNIVERSITY OF BUENOS AIRES**, Bs.As., Argentina.
Ph.D. Student, Teacher Assistant.

Responsible for GC/MS analysis of the samples generated from the Chemistry Department. Set-up, calibration, validation and troubleshooting.
T.A. in the graduate course "Theoretical and practical bases of HPLC and Capillary Electrophoresis".
Extensive use of spectroscopic (NMR, UV, FT-IR, MS) and chromatographic (HPLC, GC) methods of analysis and structure determination, including, setting-up, calibration, validation, troubleshooting and data interpretation.

ACCOMPLISHMENTS:
Developed new synthetic strategy for the preparation of novel brain mapping agents for SPECT. (See publications).
Developed methods for HPLC, LC/MS, GC/MS and UV-VIS analysis of a family of Phenyl and indoleamines.

April 1997- Dec. 1999 **TECHNONUCLEAR S.A.**, Buenos Aires, Argentina.
Scientist. Research and Development Laboratory

Developed methods for synthesis, scaling-up and production of generic brand pharmaceuticals.
Trained personnel for laboratory research, production and Quality Control, following cGMP and USP protocols.

ACCOMPLISHMENTS:

Developed methods for preparation under cGMP and quality control of several generic brand pharmaceuticals.

September 1990- April 1994 **NATIONAL INSTITUTE OF ONCOLOGY**, Havana, Cuba.
Scientist

Trained and supervised four laboratory technicians in the production and quality control of radiopharmaceuticals.

ADDITIONAL SKILLS:

English, Spanish and Russian Languages.

SKILLED IN THE OPERATION OF THE FOLLOWING:

Gas Chromatography: GC/MS Shimadzu QP-5000 and QP-5050, SPB-1 Supelco column, Hewlett-Packard 6890 series, HP-5MS column/FID.
HPLC: LKB VMB 2141 Pharmacia, RP-18 column, UV detection; Waters 2690; Finnigan (Single quadrupole and LCQ-advantage ion trap)and Hitachi LC/MS (APCI), Hitachi (SSI, ESI).
Infrared: Mattson 3000 FTIR, Nicolet Magna-IR 560.
UV-VIS and Fluorescence: Hewlett-Packard 8453, Shimadzu UV-2101 and Perkin-Elmer LS 50B.
NMR: Bruker AC-200 MHz and 400 MHz.,
Computers: Turbochrom, Hitachi, Millenium, Masslynx and ChemStation. Excel, Word, Power Point, Chemwind.

EDUCATION: FLORIDA INTERNATIONAL UNIVERSITY, Miami, USA.
Postdoctoral Research. NIH Project.
UNIVERSITY OF BUENOS AIRES, Argentina
Ph.D. in Organic Chemistry
MOSCOW STATE UNIVERSITY, Moscow, Russia.
M.S. in Radiochemistry.

AFFILIATIONS:

American Chemical Society

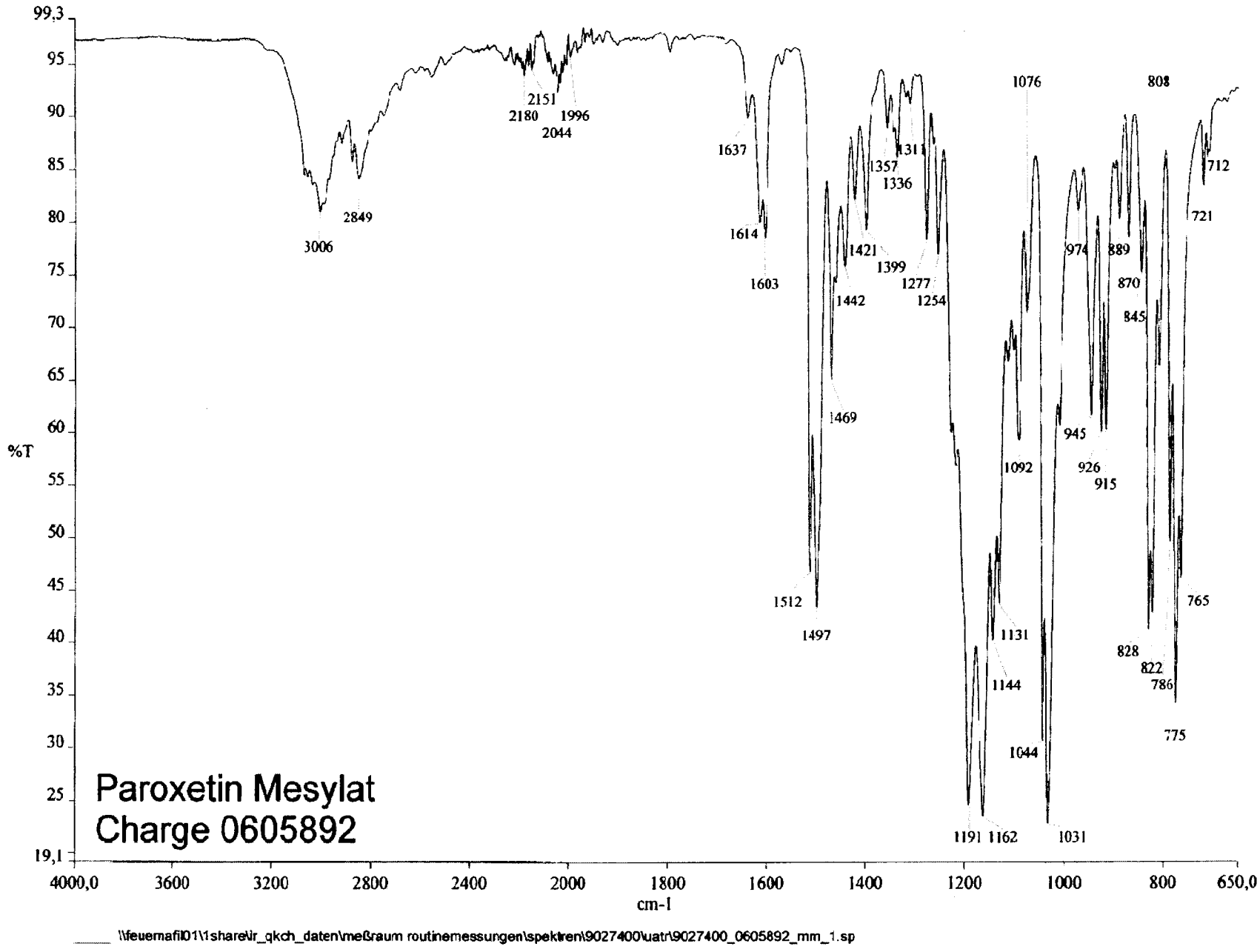
PUBLICATIONS:

- J. Sintas, V. Nguyen, D. Cloer, J. Ducan, S. Bonne, d. Kanios, J. Mantelle. The use of Acrylic PSA Concentration, Permeation Enhancement and Backing Material Selection to Control the drug delivery of a Benzothiazole in Transdermal Drud Delivery Systems (TDDSs). Oct. 2006.
- J. Sintas, R. Hartwig, S. Bonne. Transdermal Drug Delivery of Ketoprofen Esters. Nov. 2005.
- David A. Becker, Jose A. Sintas. Synthesis of Cyclic Azulenyl Nitrones as Potential Free Radical Trapping Fluorescent Probes. *J. Am. Chem. Soc.* (2002).
- Jose A. Sintas, Norberto J. Macareno, Arturo A. Vitale. Synthesis of 8-[^{10}B]-dihydroxyboryl-harmine, a potential agent for BNCT. *J. Lab. Comp. Rad.* **43**, 97 (2000).
- Jose A. Sintas, Arturo A. Vitale. Iodination, Radioiodination and Spectroscopic Identification of β-Carboline derivatives. *J. Lab. Comp. Rad.* **42**, 409 (1999).
- José A. Sintas, Arturo A. Vitale. Synthesis Of ^{131}I Derivatives of Phenyl-alkylamines for Brain Mapping. *J. Lab. Comp. Rad.* **41**, 53 (1998).
- José A. Sintas, Arturo A. Vitale. Synthesis of derivatives of ^{131}I- Indol-alkylamines for Brain Mapping. *J. Lab. Comp. Rad.* **40**, 607 (1997).
- José A. Sintas de Blanck, N. Rovnij. Labeling and Preclinical Studies of anti-EGF-Receptor Monoclonal Antibodies. *Diagnostic Oncology*. 251 (1996).
- J. A. Sintas, N. Rovnij, J. P. Oliva, J. Choy, R. Cárdenas. Radiopharmaceuticals for the Renal System: Kits for their labeling, Quality Control and Preclinical Evaluation. *Revista Española de Medicina Nuclear*. **11**, 127 (1992).

RELEVANT COURSEWORK:

- LCMS Method Development. PITCON. Orlando Fl 2006.
- LCQ Maintenance. Thermo Electron Institute. April 2005. West Palm Beach, Fl
- LCQ Operation. Thermo Electron Institute. April 2004. West Palm Beach, Fl.
- Millennium 3.2 October-November 2003. Corona, CA.
- Mass Spectrometry Seminar series. Summer 2003. Fort Lauderdale. Fl.
- Computational Chemistry. University of Buenos Aires (UBA). 04/99-06/99.
- Theoretical and practical bases of HPLC and Capillary Electrophoresis. UBA. 08-12/98.
- Environmental Chemistry. UBA. 08/98-12/98.
- Selected Topics in Organometallic Redox Chemistry. Stuttgart University-UBA. 03/98.
- Instrumental Analysis in Organic Chemistry. (NMR, IR, UV, MS, etc.). UBA. 03-06/97.
- Advanced Organic Chemistry. University of Buenos Aires. 03-06/97.
- Natural Products with Pharmacological Activity. University of Havana. 12/93-04/94.
- Molecular Immunology. Havana. Cuba. 09/93-12/93.
- Radiopharmacy and Radiopharmaceuticals. IAAE. Madrid. Spain. 04/92-05/92.
- Synthesis of Modern Radiopharmaceuticals. IAAE. Buenos Aires. Argentina. 03/92.

APPENDIX B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\\feuernafil01\1share\ir_qkch_daten\meßraum routinemessungen\spektren\9027400\uatr\9027400_0605892_mm_1.sp

APPENDIX C

date: Tuesday, July 15, 2008

Informe de identificacion por IR

instrument serial number: 75050

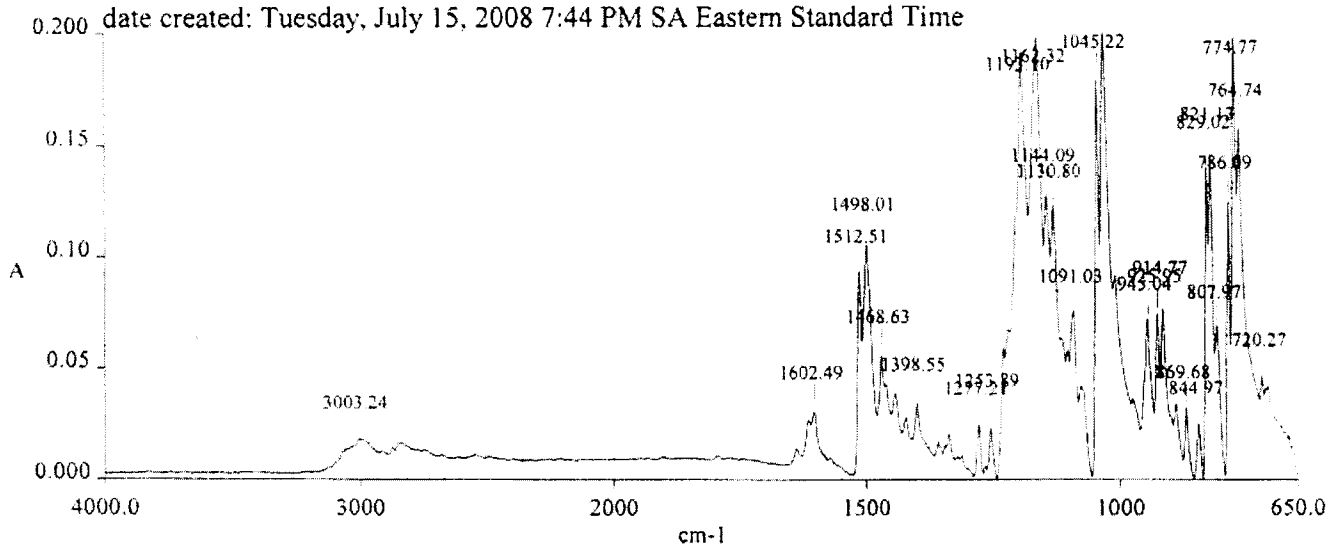
description: CCSL: POT.mes.1745.063.068

instrument model: Spectrum 100

spectrum pathname: C:\pel_data\spectra\AProd terminados e intermediarios\POT.mes\POT.mes 063.001.sp

analyst: Carolina Amatto (CA)

ir accessory: HATR



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comments: LOTE: POT.mes.063.068

Compare - SRS.POT.mes Lote 28935.001.sp

File: Correlation: Factor: Description:

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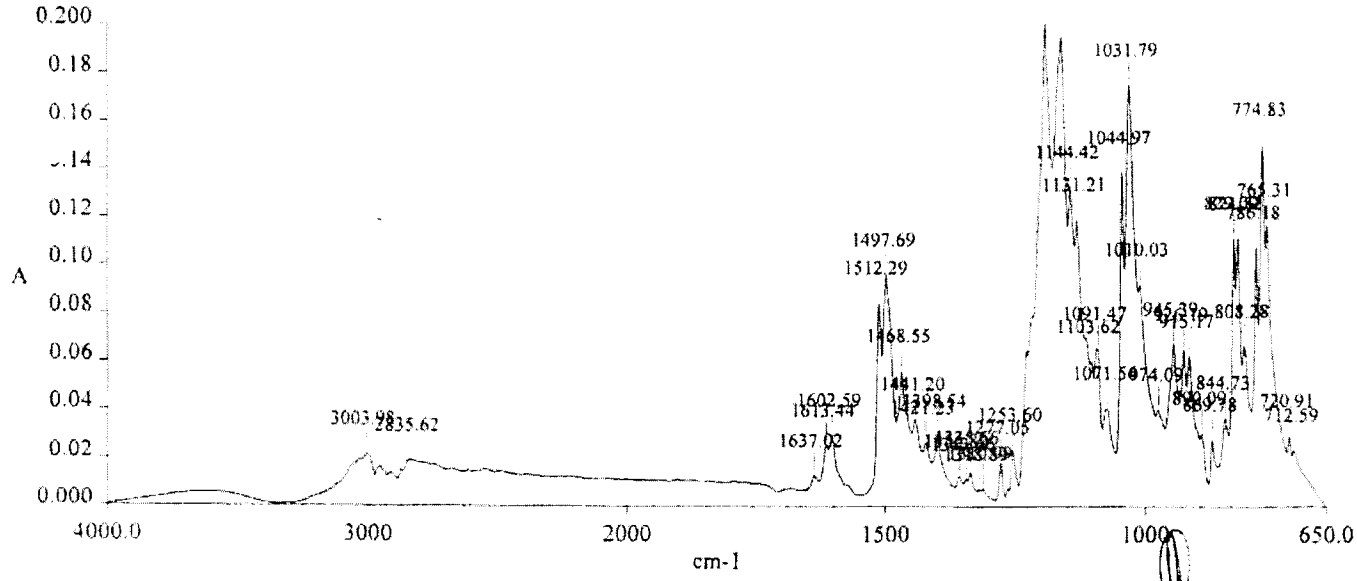
0.9745 1.7753 CCSL: POT.mes.1745.063.068



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Firma:

Fecha: 15/07/08

comments:

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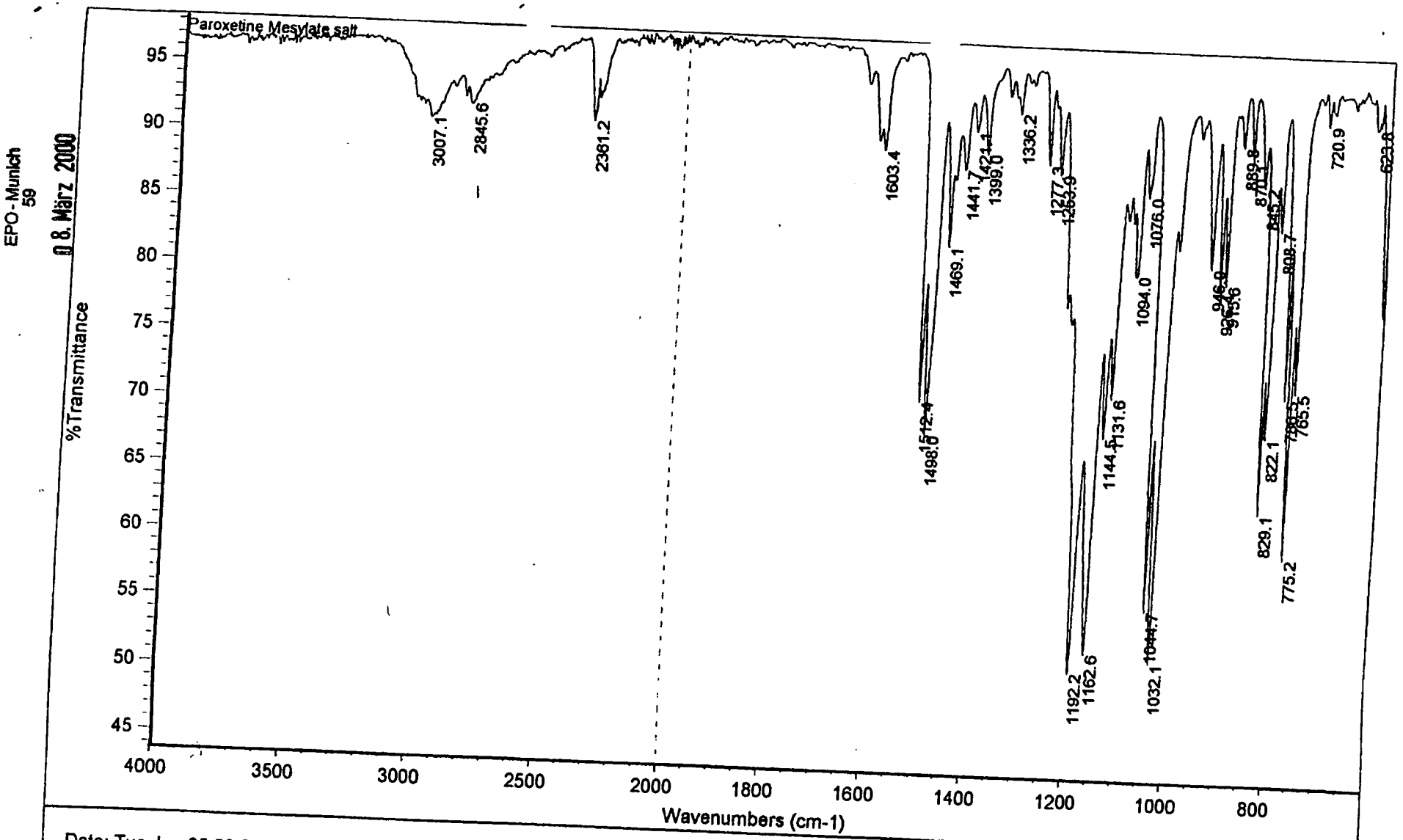
APPENDIX D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08. März 2000
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1498.0
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915.6
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845.2
829.1
822.1
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Scans: 32
Resolution: 4.000
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Example 3 ATR
Davidle O'Keeffe 5-Jan-99